Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

# Role of mineralocorticoid receptor activation in cardiac diastolic dysfunction☆

Guanghong Jia [a,b], Yan Jia [a], James R. Sowers [a,b,c,*]

[a] Diabetes and Cardiovascular Center, University of Missouri School of Medicine, Columbia, MO, 65212, USA
[b] Research Service, Harry S Truman Memorial Veterans Hospital, Research Service, 800 Hospital Dr, Columbia, MO 65212, USA
[c] Department of Medical Pharmacology and Physiology, University of Missouri School of Medicine, Columbia, MO, 65212, USA

ARTICLE INFO

*Article history:*
Received 11 August 2016
Received in revised form 29 September 2016
Accepted 26 October 2016
Available online xxxx

*Keywords:*
Mineralocorticoid receptors
Diastolic heart failure
Obesity
Insulin resistance
Females

ABSTRACT

The prevalence of cardiac diastolic dysfunction and heart failure with preserved ejection, a major cause of morbidity and mortality in the western world, is increasing due, in part, to increases in obesity and type 2 diabetes. Characteristics of cardiac diastolic dysfunction include increased myocardial stiffness and impaired left ventricular (LV) relaxation that is characterized by prolonged isovolumic LV relaxation and slow LV filling. Obesity, insulin resistance and type 2 diabetes, especially in females promote activation of mineralocorticoid receptor (MR) signaling with resultant increases in oxidative stress, maladaptive immune responses, inflammation, and impairment of coronary blood flow and cardiac interstitial fibrosis. This review highlights findings from the recent surge in cardiac diastolic dysfunction research. To this end it highlights our contemporary understanding of molecular mechanisms of MR regulation by genetic, epigenetic and posttranslational modifications and resultant cardiac diastolic dysfunction associated with insulin resistance, obesity and type 2 diabetes. This review also explores potential preventative and therapeutic strategies directed in the prevention of cardiac diastolic dysfunction and heart failure with preserved ejection. This article is part of a Special Issue entitled: Genetic and epigenetic control of heart failure edited by Dr. Jun Ren & Yingmei Zhang.



## 1. Introduction

The prevalence of heart failure, a major cause of morbidity and mortality in the western world, is increasing due, in part, to increases in obesity diabetes and hypertension. A large community-based analysis of 5881 participants from the Framingham Heart Study found that obese subjects have a doubling of the risk for heart failure [1,2]. After adjustment for established risk factors, such as diabetes, hypertension, and dyslipidemia, there was an increase in the risk of heart failure of 5% for men and 7% for women for each increment of 1 in body mass index [1,2]. Also, the Framingham Heart Study found insulin resistance increases risk of heart failure 2–8 fold in patients with diabetes [3–5]. Obesity/diabetes-induced cardiac dysfunction often progresses through an initial subclinical period characterized by subtle structural and functional abnormalities, for example, diastolic relaxation through to severe diastolic heart failure with normal ejection fraction followed by systolic dysfunction accompanied by heart failure with reduced ejection fraction [6]. Thus, cardiac diastolic dysfunction (DD) is one of the early functional cardiac abnormalities observed in obesity, diabetes and associated cardiovascular disease (CVD) and is an independent risk predictor of CVD events [1,6]. Changes in myocardial metabolism of glucose and fatty acids may be responsible for structural changes in the myocardium, such as cardiac hypertrophy, collagen deposition, and interstitial and peri-vascular fibrosis. All these structural changes lead to cardiac DD and heart failure with preserved ejection fraction [6].

Increased activation of the renin–angiotensin– aldosterone system in states of insulin resistance and/or obesity has an important role in the pathogenesis of various CVD, including cardiac DD and heart failure [1]. Epidemiological studies support an important relationship between elevated aldosterone levels and increased risk rates of cardiovascular disease (CVD), and it is well-established that inhibitors of mineralocorticoid receptor (MR) activation reduce CVD events [7]. Large randomized controlled trials such as RALES, EPHESUS, and EMPHASIS have demonstrated that MR antagonist decrease mortality and morbidity in both mild and moderately severe heart failure [8]. Furthermore, a randomized, controlled clinical trials evaluated the efficacy of MR antagonists in patients with cardiac DD or heart failure with preserved ejection fraction

☆ This article is part of a Special Issue entitled: Genetic and epigenetic control of heart failure edited by Dr. Jun Ren & Yingmei Zhang.

* Corresponding author at: University of Missouri, D109 Diabetes Center HSC, One Hospital Drive, Columbia, MO 65212, USA.
*E-mail address:* sowersj@health.missouri.edu (J.R. Sowers).

http://dx.doi.org/10.1016/j.bbadis.2016.10.025
0925-4439/

and found that MR antagonists inhibited cardiac fibrosis and improved cardiac DD, implicating MR signaling as a key contributor of cardiac DD and heart failure [9]. MRs are expressed in coronary vessel endothelial cells (ECs) and vasular smooth muscle cells (VSMCs), cardiomyocytes, fibroblasts, as well as on immune cells [10,11] (Fig. 1). Enhanced activation of MRs by aldosterone or glucocorticoids impairs insulin metabolic signaling, induces oxidative stress, induces inflammation and subsequently prompts cardiovascular abnormalities in patients with obesity, insulin resistance and diabetes mellitus who typically exhibit a high prevalence of cardiac DD [11] (Fig. 1). Research into the pathophysiology involved in the evolution of DD has demonstrated the importance of systemic and cardiac insulin resistance, impaired coronary microcirculation, oxidative stress, as well as maladaptive immune responses i, [12,13]. However, the precise role of enhanced activation of MRs in the pathogenesis of DD in insulin resistance, type 2 diabetes, and obesity is still yet to be elucidated. In the present review, we will focus on recent studies examining the pathophysiological processes by which MR activation contributes to cardiac DD and CVD, as well as the contemporary understanding of potential therapeutic strategies.

## 2. Pathophysiology of cardiac DD

Both increased myocardial fibrosis and stiffness and impaired left ventricular (LV) relaxation with preserved ejection characterize cardiac DD. This cardiac abnormality includes prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness [14,15]. One factor that may be involved in DD pathology is LV hypertrophy (LVH) which increases the ratio of myocardial mass to volume, and the hypertrophy level is a critical determinant of chamber stiffness. LVH often leads to a vicious cycle of greater LV filling pressures and poor LV compliance [15]. Furthermore, a characteristic feature of diastolic heart failure with preserved ejection is slow LV relaxation, which may reduce LV stroke volume, especially at high heart rates [15]. LV relaxation is dependent on both nitric oxide (NO) signaling and sarcoplasmic reticular calcium ($Ca^{2+}$) reuptake [11]. Endothelium NO synthase (eNOS) activation increases bioavailable NO which diffuses into the cardiomyocytes, interacts with soluble guanylate cyclase to generate the second messenger cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). The soluble cGMP activates cyclic nucleotide-dependent protein kinase G (PKG) [11]. PKG, a kinase involved in phosphorylating a number of proteins, hyperpolarizes the cell membrane, regulates $Ca^{2+}$ concentrations and sensitization, and causes actin filament and myosin dynamic alterations, and subsequently results in cardiomyocyte relaxation [11]. Meanwhile, NO/PKG/cGMP signaling can phosphorylate the large stiffness protein titin by changing the ratio of titin isoform N2BA:N2B expression which, in turn, decreases cardiac stiffness and improves relaxation [16]. In this regard, Titin is a sarcomeric protein that functions as a molecular spring and LV relaxation function [17]. Alternative splicing of titin isoforms gives the two isoforms: the larger and more compliant N2BA containing both N2A and N2B segments and the smaller N2B isoform containing only the N2B segment in heart [17]. Recently the titin splicing factor RBM20 was discovered to regulate cardiac function in a mouse model of heart failure [18]. Inactivating RBM20 results in upregulation of compliant titin isoforms and a large reduction in cellular passive stiffness whereas extracellular matrix (ECM)-based stiffness is unaffected [18]. These changes were associated with improvement of LV diastolic chamber compliance, concentric remodeling and exercise tolerance [18]. One study also found that an increase of cardiac titin isoforms N2BA:N2B expression ratio was present in 20 heart failure patients [19], suggesting that the ratio of cardiac titin isoforms N2B (stiffness) and large N2BA (compliant) plays a key role in cardiac compliance. Thus, alterations in titin biology can lead to both cardiac stiffness and impairment of relaxation.

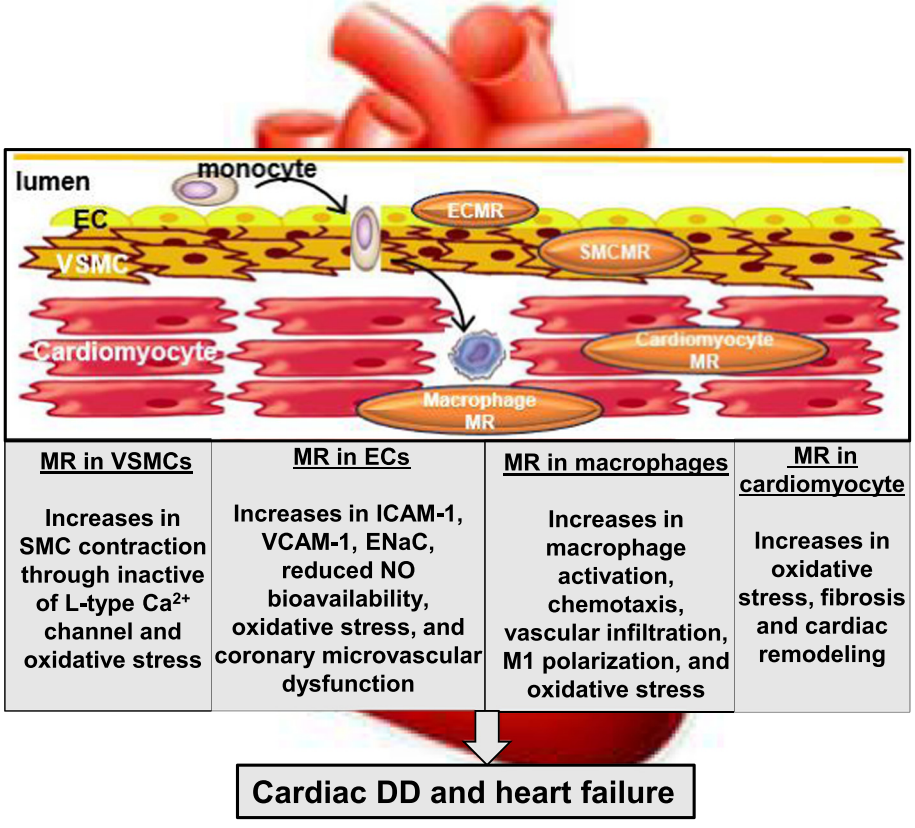


**Fig. 1.** Depiction of molecular mechanism in the enhanced MR signaling-induced cardiac DD and heart failure. Abbreviations: MR, mineralocorticoid receptor; EC, endothelial cells; VSMC, vascular smooth muscle cells; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ENaC, epithelial sodium channel; NO, nitric oxide; DD, diastolic dysfunction.

Please cite this article as: G. Jia, et al., Role of mineralocorticoid receptor activation in cardiac diastolic dysfunction, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbadis.2016.10.025